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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,123	01/06/2006	Hideyuki Sato	TC0003	8847

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EXAMINER	
LEESER, ERICH A	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
05/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,123	SATO ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-6-06 & 5-12-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group IV in the reply filed on March 10, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant also elected the species of Example 1(d) found on page 21, lines 5-10 of the specification.

Priority

Examiner acknowledges that this application is a 371 of PCT/US04/21701, filed on July 7, 2004 and which claims benefit of domestic priority to 60/485,365, filed on July 8, 2003.

Information Disclosure Statement

The references contained in the IDSs dated January 6, 2006 and May 12, 2006 are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to inhibit hYAK3 and/or MK2 proteins in a mammal or treat a disorder selected from neutropenia;

cytopenia; anemias, including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke; and ischemia reperfusion injury using an effective amount of a compound corresponding of formula I or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to tricyclic pyrimidinyl kinase inhibitors which allegedly can inhibit hYAK3 and/or MK2 proteins in a mammal or treat a disorder selected from neutropenia; cytopenia; anemias, including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke; and ischemia reperfusion injury using an effective amount of a compound corresponding of formula (I); and pharmaceutical compositions thereof.

The state of the prior art:

Art later than the filing date of the instant invention shows the lack of understanding in the synthetic organic chemistry community as to the effective inhibition of MK2 proteins in mammals: "The protein kinases checkpoint kinase 1 (Chk1), checkpoint kinase 2 (Chk2), and mitogen-activated protein kinase-activated protein kinase 2 (MK2) have all been shown to be involved in cell cycle checkpoint control. Recently, cell cycle checkpoint abrogation has been proposed as one way to sensitize cancer cells to DNA-damaging agents due to the expected induction of mitotic catastrophe. Due to their overlapping substrate spectra and redundant functions, it is still not clear which kinase is mainly responsible for the cell cycle arrests conferred by clinically relevant chemotherapeutics. Thus, the issue remains about which kinase is the most therapeutically relevant target and, more importantly, whether multiple kinases might need to be targeted to achieve the best efficacy in light of recent studies showing superior efficacy for pan-receptor tyrosine kinase inhibitors. To clarify this issue, we investigated the roles of the three kinases in response to different genotoxic stresses through small interfering RNA-mediated specific target knockdowns. Our result showed that *only* the down-regulation of *Chk1, but not* of Chk2 or *MK2*, abrogated camptothecin- or 5-fluorouracil-induced S-phase arrest or doxorubicin-induced G(2)-phase arrest. This was followed by mitotic catastrophe and apoptosis. Moreover, double inhibition of Chk1 and Chk2 failed to achieve better efficacy than Chk1 inhibition alone; surprisingly, inhibition of MK2, in addition to Chk1 suppression, partially reversed the checkpoint abrogation and negated mitotic catastrophe. We further showed that this is due to the fact that in MK2-deficient cells, Cdc25A protein, which is critically required for the mitotic progression following checkpoint abrogation, becomes greatly depleted. In summary, ***our findings show that Chk1 is the only relevant checkpoint kinase as a cancer drug target***

and inhibition of other checkpoint kinases in addition to Chk1 would be nonproductive." (Emphasis added). Xiao, et al., *Differential roles of checkpoint kinase 1, checkpoint kinase 2, and mitogen-activated protein kinase-activated protein kinase 2 in mediating DNA damage-induced cell cycle arrest: implications for cancer therapy.* Molecular Cancer Therapeutics, (2006 Aug) Vol. 5, No. 8, pp. 1935-43.

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of formula (1) would be useful to inhibit hYAK3 and/or MK2 proteins in a mammal or treating a disorder selected from neutropenia; cytopenia; anemias, including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke; and ischemia reperfusion injury.

Amount of guidance/working examples:

Beginning on page 39 Applicant provides "Biological Methods and Data" ending on page 42. These examples in the specification; however, do not definitively prove that the instant compounds can be used to inhibit hYAK3 and/or MK2 proteins in a mammal or treating a disorder selected from neutropenia; cytopenia; anemias, including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure;

stroke; and ischemia reperfusion injury using an effective amount of a compound corresponding of formula (I).

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient to inhibit hYAK3 and/or MK2 proteins in a mammal or treating a disorder selected from neutropenia; cytopenia; anemias, including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke; and ischemia reperfusion injury with an effective amount of a compound of formula (I), one of ordinary skill in the art, even with a high level of skill, is unable to use the instant compounds to inhibit hYAK3 and/or MK2 proteins in a mammal or treating a disorder selected from neutropenia; cytopenia; anemias, including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke; and ischemia reperfusion injury as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to use the compounds of formula (1) to inhibit hYAK3 and/or MK2 proteins in a mammal or treating a disorder selected from neutropenia; cytopenia; anemias,

including cancer; polycythemia; myelosuppression; arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke; and ischemia reperfusion injury without undue experimentation.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the protein kinase inhibitors such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before infection occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 23, page 7 to line 4, page 8 lists the diseases Applicant intend to treat. 3) There is no working

example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical internal medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become infected before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in renal, cardiac, brain, bone and skin diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of anemic diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent anemias generally. That is, the skill is so low that no compound effective generally against anemic disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by formula I.

The Examiner suggests deletion of the phrase "or preventing" from claim 4.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making solvates of the claimed invention. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The nature of the invention:

The invention is drawn to compounds of formula I (and methods for using same), or a "salt, solvate, or a physiologically functional derivative thereof." The specification is not adequately enabled to show how to make solvates of compounds of formula I. The compounds of formula I embrace tricyclic pyrimidinyl compounds substituted with variable groups R, R^1, and R^2.

Even a cursory calculation of the number of compounds embraced in the instant formula I would result in thousands of compounds. This is of course far more compounds than the specification enables one skilled in the art to make. Thus, the genus embraced in claim 1 is too large and there is no teaching of any solvate of this large genus.

The state of the prior art:

A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it

is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

The predictability or lack thereof in the art:

For the reasons stated *supra*, the solvates as applied to the above-mentioned compounds claimed by the Applicant are not art-recognized compounds and hence there should be an enabling disclosure in the specification with working example(s).

The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvates of the instant compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that the instant compounds formed solvates. Hence it is clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance.

The presence or absence of working examples:

There is no working example of any solvate formed. These cannot be simply willed into existence. "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that solvates of these compounds exist and therefore can be made.

The breadth of the claims:

The breadth of the claims include all of the perhaps thousands of compounds of formula I of claim 1 as well as the presently unknown list of potential solvate derivatives embraced by these terms. The term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the solvates of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The quantity of experimentation needed

The specification has insufficient support, as noted *supra*, for the desired solvates of the compounds of formula I. As noted above, the genus embraces thousands of compounds and hence the breadth of the claims is broad. The quantity of experimentation needed would be an undue burden on one skilled in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated *supra*. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvates of the compounds of formula I embraced in the instant claims.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private

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